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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/535,630	11/04/2005	Gerhard Hoefle	930008-2200	9251
<div>7590 Ronald R Santucci Frommer Lawrence &amp; Haug 745 Fifth Avenue New York, NY 10151</div>				
08/10/2009				
EXAMINER				
MABRY, JOHN				
ART UNIT		PAPER NUMBER		
1625				
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

### Office Action Summary

**Application No.**

10/535,630

**Applicant(s)**

HOEFLE ET AL.

**Examiner**

JOHN MABRY

**Art Unit**

1625

**Period for Reply** -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 22 May 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-82 is/are pending in the application.
- 4a) Of the above claim(s) 3-67 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1, 2 and 68-82 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-8508)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

***Response to Applicant's Remarks***

In view of this response, the status of the rejections/objections of record is as follows:

***Status of the Claims***

Claims 1, 2 and 68-82 are pending and rejected.

Claims 3-67 directed towards non-elected subject matter.

***35 USC § 112 Rejection(s)***

The 112-2<sup>nd</sup> rejection of claims 2, 68, 69 and 72 regarding the phrases "preferably" and "especially" have been overcome in view of Applicants amendment to the claims.

The 112-1<sup>st</sup> rejection of claims 1, 2 and 68-82 regarding the scope of enablement for "R10 and T" have not been overcome in view of Applicants amending the claims. R10 and T being the entire scope as claimed.

Applicant argues that there is "substantial guidance" in the Specification. Examiner respectfully disagrees. As clearly set forth in previous Office Action, there is not sufficient guidance (in the Specification) on how to make the claimed compounds of Formula I, especially where said variables are "heteroaryl". As set forth in previous Office Action, there is no guidance nor working examples where said variables equal any type of heteroaryl chemical moiety.

The widely acceptable definition of the term "heteroaryl" is designating a closed-ring structure, usually of either 5 or 6 members, in which one or more of the atoms in the ring is an element other than carbon is replaced with sulfur, oxygen or nitrogen, etc (see Hawley's Condensed Chemical Dictionary, 14<sup>th</sup> Ed., John Wiley & Sons, Inc. 2001, New York).

Applicant states that guidance is provided in Figure 7 (sheet 7/9) which "clearly shows how derivatives of compounds are prepared wherein R4 is a group other than H".

While this statement is theoretically true, as set forth in previous Office Action, the availability of starting materials and the complexity and unpredictability of synthetic organic chemistry (see Dorwald) would certainly imposed an undue burden to one of ordinary skill in the art on how to make such claimed compounds.

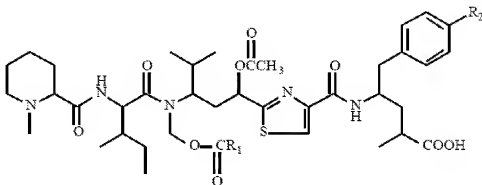
**Note:** Examiner provided additional reference(s) only rebut Applicant's arguments and to further support Examiner's rejection of record.

### ***Claim Rejections - 35 USC § 102***

Claims 1, 68 and 72 rejections are withdrawn under 35 U.S.C. 102(b) as being anticipated by Hamel et al (Curr. Med. Chem. – Anti-Cancer Agents, 2002, Vol. 2, No. 1). Applicant's amendment necessitated the new ground(s) of rejection as being obvious over Hamel et al (Curr. Med. Chem. – Anti-Cancer Agents, 2002, Vol. 2, No. 1) in view of Wolff et al Burger's Medicinal Chemistry and Drug Discovery, 5<sup>th</sup> Edition, Volume 1: Principles and Practice 1995, 974-977 – claims 1, 68, 72, 76, 78 and 82.

Page 4

Page 4



## Tubulysins

	R <sub>1</sub>	R <sub>2</sub>
A	CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	OH
B	CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	OH
C	CH <sub>2</sub> CH <sub>3</sub>	OH
D	CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	H
E	CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	H
F	CH <sub>2</sub> CH <sub>3</sub>	H

Page 4

Page 4

compounds are simply prodrugs of the compounds of the prior art. Wolff et al describes scientific reasoning of why a skill artisan in the relative art would be motivated to convert a carboxylic acid to an alkyl ester. Hamel clearly describes pharmaceutical use of Tubulysins for the treatment of human disease (see Introduction and entire reference). Wolff clearly describes that a prodrug may need to be formed when difficulties arise related to the pharmacokinetics of the active drug. Wolff continues to provide considerations for prodrug design and why one of ordinary skill in the art would be motivated to create a prodrug: a) identification of the drug delivery problem; b) identification of the physicochemical properties required for optimal delivery; and c) selection of a prodrug derivative that has proper physicochemical properties and that will be cleaved in the desired biological compartment (see Section 9.1 on page 975 and entire reference).

Again, the claimed compounds are simply ester derivatives (prodrugs) of the known compound of the prior art. It is very well known that the formation of a prodrug can alleviate potential problems related to pharmacokinetics of the active drug for targeting.

Claims 1, 68 and 72 rejections are withdrawn under 35 U.S.C. 102(b) as being anticipated by Sasse et al (Journal of Antibiotics 2000, 53, 879-885). Applicant's amendment necessitated the new ground(s) of rejection as being obvious over Sasse et al (Journal of Antibiotics 2000, 53, 879-885) in view of Wolff et al Burger's Medicinal

Chemistry and Drug Discovery, 5<sup>th</sup> Edition, Volume 1: Principles and Practice 1995, 974-977 for the same reasons as given above – claims 1, 68, 72, 76, 78 and 82.

Claims 1, 68 and 72 rejections are withdrawn under 35 U.S.C. 102(b) as being anticipated by Hoefle et al (DE 10008089 A1) (PTO-1449). Applicant's amendment necessitated the new ground(s) of rejection as being obvious over Hoefle et al (DE 10008089 A1) (PTO-1449) in view of Wolff et al Burger's Medicinal Chemistry and Drug Discovery, 5<sup>th</sup> Edition, Volume 1: Principles and Practice 1995, 974-977 for the same reasons as given above – claims 1, 68, 72, 76, 78 and 82.

Claims 1, 68 and 72 rejections are withdrawn under 35 U.S.C. 102(b) as being anticipated by Hoefle et al (DE 19638870 A1) (PTO-1449).

Applicant's amendment necessitated the new ground(s) of rejection as being obvious over Hoefle et al (DE 19638870 A1) (PTO-1449) in view of Wolff et al Burger's Medicinal Chemistry and Drug Discovery, 5<sup>th</sup> Edition, Volume 1: Principles and Practice 1995, 974-977 for the same reasons as given above – claims 1, 68, 72, 76, 78 and 82.

The declaration under 37 CFR 1.132 filed May 22, 2009 does not overcome the rejections of being obvious over rejections as set forth above.

Examiner acknowledges the L929 IC50 results in Table on page 2 of declaration. However, this is not sufficient to overcome the obviousness rejection of record as set forth above.

The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR* noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. The Court quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006), stated that “[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *KSR*, 550 U.S. at \_\_\_, 82 USPQ2d at 1396. Exemplary rationales that may support a conclusion of obviousness include:

- (A) Combining prior art elements according to known methods to yield predictable results;
- (B) Simple substitution of one known element for another to obtain predictable results;
- (C) Use of known technique to improve similar devices (methods, or products) in the same way;
- (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;
- (E) “Obvious to try” – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;
- (F) Known work in one field of endeavor may prompt variations of it for use in



either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art;

(G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention. See MPEP § 2143 for a discussion of the rationales listed above along with examples illustrating how the cited rationales may be used to support a finding of obviousness. See also MPEP § 2144- §2144.09 for additional guidance regarding support for obviousness determinations.

The aforementioned reasons above describe rationales that support a conclusion of obviousness based upon the KSR International Co. v. Teleflex Inc. decision. Letters (A) - (E) rationale is supported above.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

### ***Conclusion***

Applicant is respectfully reminded that it is required that all claims be amended to elected group. Examiner also warns Applicant not to introduce new matter when amending.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John Mabry, PhD whose telephone number is (571) 270-1967. The examiner can normally be reached on M-F from 9am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's primary examiner can be reached at (571) 272-0684, first, or the Examiner's supervisor, Janet Andres, PhD, can be reached at (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Application/Control Number: 10/535,630  
Art Unit: 1625

Page 10

/John Mabry/  
Examiner  
Art Unit 1625

/Rita J. Desai/  
Primary Examiner, Art Unit 1625